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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,468	04/02/2001	Arthur M. Krieg	C1039/7049(HCL/MAT)	9046

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WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2211

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	12

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/824,468	KRIEG ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5-7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Amendment filed April 8, 2003 in Paper No. 11.

Claims 22-43 are pending in the instant application.

Specification

Applicants Amendment to the first paragraph of the specification to update the status of related applications is acknowledged.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 22-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is withdrawn in view of Applicants arguments filed April 8, 2003 in Paper No. 11.

Claims 22-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained (*in part*) for the reasons of record set forth in the previous Office Action filed October 3, 2002 in Paper No. 9.

Applicants argue that the Examiner's reliance in objecting to the specification and claims upon a purported failure of the specification to enable the use of CpG and cytokine in any organism is misplaced. Applicants argue that the specification provides guidance with respect to the administration of the compounds of the invention to different subjects, and further guidance is provided concerning routes of administration. This is found persuasive.

Applicants argue that methods for delivering cytokines and CpG oligonucleotides to subjects have been described in many publications and patents. Applicants rely on specific patents for examples. Applicants further rely on two references submitted as Exhibits 1 and 2, which demonstrate the effectiveness of CpG in stimulating an immune response in non-human animals. The first, Rankin et al. (Vaccine, 2002) demonstrates that *in vivo* administration of CpG oligonucleotides significantly reduced viral shedding in calves. The second, Rankin et al. (Nucleic Acid Drug Dev, 2001) demonstrated that CpG motifs induced an immune response *in vivo* in sheep. This is found persuasive.

Applicants further argue that the Examiner's citation of Krieg and Wagner for the proposition that the cytokine response to CpG is greater in mice than humans or primates is taken out of context. Applicants also argue that the Examiner's citation of Weiner et al. cited for the proposition that the direct effects of CpG OND on T cells is controversial is irrelevant. Applicants further argue that the Examiner's reference of Branch cited to illustrate the state of the art of gene therapy and the statement that targeting nucleic acids, like CpG, fall into the broad area known as gene therapy methods, is not scientifically correct. This is found persuasive.

However, Applicant has failed to address another reference cited by the Examiner for the proposition that immunostimulatory DNA inhibit specific Th2 cytokines. More specifically, Broide et al. (Journal of Immunology, 1998 Vol.161:7054-7062) was relied upon as disclosing that an immunostimulatory DNA containing a CpG motif significantly inhibited Th2 cytokines, IL-5 and IL-3 in mice (see Abstract). This disclosure shows an antagonist effect of immunostimulatory CpG motif sequences on IL-5 and IL-3 production (see Table I). The results of Broide et al. indicate that much work needs to be done to determine the biological effects of CpG oligonucleotides in whole organisms and to elucidate the role of cytokines in inducing a synergistic immune response using a combination of an immunostimulatory CpG oligonucleotide, for example.

Applicants further argue that no evidence has been provided to support the Examiner's assertion that one of skill in the art would not accept on its face the examples disclosed in the specification as being representative or correlative of the subject matter of the full scope of the invention. Applicants argue that the instant specification as filed provides sufficient guidance to teach of skill in the art how to make and use the compositions which are useful in the invention. Applicants further argue that the instant specification as filed provides actual working examples to demonstrate that the invention does work. Applicants point to specific pages in the specification where descriptions are made to methods of delivering the compounds of the instant invention, to produce an immune response.

This is not found persuasive because the instant specification teaches the combination of GM-CSF and CpG phosphorothioated oligonucleotide 2006 shows synergy for increasing the expression of CD86 and CD40 molecule expression on dendritic cells (see Figure 9). Pending

claims 22-43 contemplate the use of IL-3, IL-5 and IL-12 as inducers of immune response synergism in a subject in combination with a CpG oligonucleotide. However, the instant specification as filed does not teach how the skilled artisan would use IL-3, IL-5 and IL-12 as an inducer of immune response synergism in a subject in combination with a CpG oligonucleotide, given the results of Broide et al. which disclosed that an immunostimulatory DNA containing a CpG motif inhibited IL-5 and IL-3 production in mice. One skilled in the art would not accept on its face the examples given in the specification of the synergism elicited by CpG phosphorothioated oligonucleotide 2006 and the cytokine GM-CSF as being correlative or representative of the induction of immune response synergism in a subject in combination with a CpG oligonucleotide and IL-3, IL-5 and IL-12. Therefore, in view of the lack of guidance in the specification regarding the use of IL-3, IL-5 and IL-12 as inducers of immune response synergism in a subject in combination with a CpG oligonucleotide, and the unpredictability associated with immunostimulatory DNA containing CpG motifs as antagonistic agents against IL-5 and IL-3 production in mice, undue experimentation would be required. Therefore, practice of the full scope of the invention would require undue experimentation.

Information Disclosure Statement

The information disclosure statements filed May 11, 2001, April 26, 2002, and September 16, 2002 are acknowledged. The information referred to therein has been considered.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
June 26, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635